

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:  
GLAXOSMITHKLINE  
Corporate Intellectual Property  
Attn. Baker, Suzanne Jane  
CN925.1  
980 Great West Road  
Brentford, Middlesex TW8 9GS  
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT AND  
THE WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY, OR THE DECLARATION

Applicant's or agent's file reference SJB/PB60264	International application No. PCT/EP2004/006604	Date of mailing (day/month/year) 30/08/2004 ✓  International filing date (day/month/year) 17/06/2004
(PCT Rule 44.1)		
31 AUG 2004 FOR FURTHER ACTION See paragraphs 1 and 4 below		
ATTY: SJB ADMIN: [initials] IPM: N/A ON: [initials] UPDATED ON: 31/8/04 ATTY CHECKED/FILE [initials]		
Applicant GLAXO GROUP LIMITED		

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

**4. Reminders**


Shortly after the expiration of **18 months** from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Dominique Hundt
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Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SJB/PB60264	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2004/006604	International filing date (day/month/year) 17/06/2004	(Earliest) Priority Date (day/month/year) 19/06/2003
Applicant  GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

**4. With regard to the title,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

3-SULFONYLAMINO-PYRROLIDINE-2-ONE DERIVATIVES AS INHIBITORS OF FACTOR XA

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. With regards to the drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/006604

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/26 C07D403/10 C07D417/12 C07D417/14 A61K31/402  
A61K31/4025 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 03/053925 A1 (GLAXO GROUP LIMITED, UK) 3 July 2003 (2003-07-03) see compounds of formula I according to claim 1 and their activity as inhibitor of factor Xa;	1-12
Y	WO 98/24784 A (CHOI SLEDESKI YONG MI ; PAULS HEINZ W (US); EWING WILLIAM R (US); SPAD) 11 June 1998 (1998-06-11) see compounds of claim 1 with definition of n as zero and their activity as inhibitor of factor Xa; ----- -/--	1-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

20 August 2004

Date of mailing of the international search report

30/08/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Traegler-Goeidel, M

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/006604

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/043981 A (KLEANTHOUS SAVVAS ; YOUNG ROBERT JOHN (GB); SENER STEFAN (GB); CHAN C) 30 May 2003 (2003-05-30) see compounds of formula I of claim 1, especially definitin of residue R6 and their activity as inhibitor of factor Xa -----	1-12
Y	US 5 958 918 A (CHOI-SLEDESKI YONG MI ET AL) 28 September 1999 (1999-09-28) see compounds o formula I of claim 1 and their activity as inhibitor of factor Xa; -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/006604

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/006604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03053925	A1	03-07-2003	NONE
WO 9824784	A	11-06-1998	US 5731315 A 24-03-1998
		AP 800 A 19-01-2000	
		AU 727810 B2 21-12-2000	
		AU 6012198 A 29-06-1998	
		BG 102725 A 31-03-1999	
		BR 9707489 A 27-07-1999	
		CA 2245699 A1 11-06-1998	
		CN 1418882 A 21-05-2003	
		CN 1213370 A ,B 07-04-1999	
		CZ 9802757 A3 13-01-1999	
		EA 1739 B1 27-08-2001	
		EP 0894088 A1 03-02-1999	
		HU 9801882 A2 28-12-1998	
		HU 9903336 A2 28-12-2000	
		JP 2000505815 T 16-05-2000	
		NO 983603 A 05-10-1998	
		OA 10823 A 24-07-2001	
		PL 328618 A1 01-02-1999	
		SI 9720019 A 28-02-1999	
		SK 122398 A3 11-01-1999	
		WO 9824784 A1 11-06-1998	
		US 6034093 A 07-03-2000	
		ZA 9710968 A 22-07-1998	
WO 03043981	A	30-05-2003	EP 1444201 A1 11-08-2004
			WO 03043981 A1 30-05-2003
US 5958918	A	28-09-1999	US 5612353 A 18-03-1997
			US 6034093 A 07-03-2000
			AP 799 A 19-01-2000
			AU 714319 B2 06-01-2000
			AU 6166996 A 30-12-1996
			BG 63628 B1 31-07-2002
			BG 102162 A 30-09-1998
			BR 9608405 A 24-08-1999
			CA 2223403 A1 19-12-1996
			EA 700 B1 28-02-2000
			EP 0853618 A1 22-07-1998
			JP 11507368 T 29-06-1999
			NO 975762 A 06-02-1998
			PL 323780 A1 27-04-1998
			SI 9620093 A 28-02-1999
			SK 160697 A3 04-11-1998
			CN 1190395 A 12-08-1998
			CZ 9703853 A3 12-05-1999
			HU 9801882 A2 28-12-1998
			OA 10752 A 04-07-2001
			WO 9640679 A1 19-12-1996
			US 5731315 A 24-03-1998



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

## PCT

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)**

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/EP2004/006604

International filing date (day/month/year)  
17.06.2004

Priority date (day/month/year)  
19.06.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D207/26, C07D403/10, C07D417/12, C07D417/14, A61K31/402, A61K31/4025, A61P7/02

Applicant  
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. ✓

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Traegler-Goeldel, M

Telephone No. +49 89 2399-8278



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006604

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006604

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**Box No. II    Priority**

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1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006604

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 11

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 11
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/006604

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
Industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes: Claims	1-10,12
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

**see form 210**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/006604

**IAP20 Rec'd PCT/PTO 19 DEC 2005**

re item III:

Claim 11 is directed to methods for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims with respect to industrial applicability.

re item V:

1. Prior art

The examining procedure is based on the documents as cited by the Applicant and as cited in the International Search Report:

- D2: WO 98/24784 A (CHOI SLEDESKI YONG MI ; PAULS HEINZ W (US); EWING WILLIAM R (US); SPAD) 11 June 1998 (1998-06-11)
- D3: WO 03/043981 A (KLEANTHOUS SAVVAS ; YOUNG ROBERT JOHN (GB); SENGHER STEFAN (GB); CHAN C) 30 May 2003 (2003-05-30)
- D4: US-A-5 958 918 (CHOI-SLEDESKI YONG MI ET AL) 28 September 1999 (1999-09-28)

2. Novelty

The claimed 3-sulfonylaminopyrrolidine-2-one derivatives differ from those disclosed in documents D3 and D4 by the residue -X-Y in position 1, i.e. by an aminoalkyl substituted (hetero)arylresidue instead of an alkylamide (D3) and aminoalkylarylresidue bound via an alkylene bridge to the 1 position (D4). Most of the present 1-aryl-3-sulfonylaminopyrrolidine-2-one derivatives clearly represents a selection from the 1-aryl-3-sulfonylaminopyrrolidine-2-one derivatives according to D2 wherein n is zero and  $X_2$  and  $X_{2a}$  together form oxo. The compounds according to present claim 1 can only be considered as being a novel selection due to the fact that there no novelty destroying examples disclosed explicitly in D2. Therefore, the subject matter of claims 1 to 12 appears to fulfil the requirements of Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Documents D2 to D4 disclose 3-sulfonylamino-pyrrolidine-2-one derivatives that are potent inhibitors of factor Xa useful in the treatment of coagulation disorders as are the 3-sulfonylamino-pyrrolidin-2-one derivatives of the present application. The closest prior art is to be seen in document D2, since present claim 1 represents clearly a selection from the compounds as generally disclosed in D2: the present compounds wherein R<sup>1</sup> is naphthalene, benzothienyl, phenyl and bithienyl fall fully under the scope of the compounds according to claim 1 of D2.

Thus, if the problem underlying the present application were to be seen in provision of further compounds that may be used as inhibitors of factor Xa, the solution of the problem must be considered as being obvious, since the claimed subject matter represents a selection from the compounds according to D2 used for exactly the same purpose. As far as the present compounds are concerned with residue R<sup>1</sup> being a -C<sub>2-3</sub>alkyl-2-thienylresidue, these compounds (as indeed all the other ones as comprised by main claim 1) represent merely a combination of the main basic 1-aryl-3-sulfonyl-pyrrolidine-2-one structure known from D2 with the sulfonylaminoresidues R<sup>6</sup> from D3 all being identical to the corresponding residues R<sup>1</sup> in present claim 1, some of which are additionally disclosed as being preferred in D4 (e.g. see claim 48).

Therefore, re that very close prior art D2 (structurally and concerning properties), the problem underlying this part of the application, the solution of which could involve an inventive step, is to be seen in the provision of compounds that do exhibit an unexpected or improved effect (of better pharmacological characteristics) compared to the closest prior art D2. The Applicant's attention is drawn to the fact, that any comparative tests should be made with compounds of the closest prior art, showing the closest possible structural similarity. If such an effect could be demonstrated (preferably by concrete experimental data) an inventive step could be acknowledged. In the present case, for instance, a compound according to D2 could be compared with a structural closest compound of the present application, differing structurally only by the essential feature, i.e. the feature which renders the subject matter novel and which an inventive step may be based on.

As yet, the present application does not fulfil the requirements of Art. 33 (3) PCT.

#### 4. Industrial applicability

No objection arises as far as the compounds according to claim 1 may be used for the

production of pharmaceutical products.

re item VI:

It is brought to the Applicant's attention that document D1, which entered the regional phase may be relevant for the consideration of novelty and for the consideration of inventive step for any subject matter entitled to the filing date only.

re item VIII:

Claim 2 is not admissible in its present form since, although it refers back to claim 1, it is not comprised by main claim 1, due to the term "each ring of which optionally contains a further heteroatom N".